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(54) Title: QUINOLINE-CONTAINING α -KETOAMIDE CYSTEINE AND SERINE PROTEASE INHIBITORS			
(57) Abstract <p>The present invention is directed to quinoline-containing α-ketoamide inhibitors of cysteine and serine proteases are disclosed. Methods for making these compounds, and methods for using the same are also disclosed.</p>			

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**QUINOLINE-CONTAINING α -KETOAMIDE CYSTEINE
AND SERINE PROTEASE INHIBITORS**

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. Provisional
5 Application Serial No. 60/061,267, filed October 7, 1997, and
U.S. Application entitled "Quinoline-containing α -ketoamide
Cysteine and Serine Protease Inhibitors" filed October 6, 1998,
the disclosures of which are hereby incorporated herein by
reference in their entirety.

FIELD OF THE INVENTION

10

This invention relates to quinoline-containing α -
ketoamide inhibitors of cysteine and serine proteases, methods
for making these compounds, and methods for using the same.

BACKGROUND OF THE INVENTION

15

Numerous cysteine and serine proteases have been
identified in human tissues. A "protease" is an enzyme
which degrades proteins into smaller components (peptides).
The terms "cysteine protease" and "serine protease" refer
to proteases which are distinguished by the presence
20 therein of a cysteine or serine residue which plays a
critical role in the catalytic process. Mammalian systems,
including humans, normally degrade and process proteins via
a variety of enzymes including cysteine and serine
proteases. However, when present at elevated levels or

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when abnormally activated, cysteine and serine proteases may be involved in pathophysiological processes.

For example, calcium-activated neutral proteases ("calpains") comprise a family of intracellular cysteine proteases which are ubiquitously expressed in mammalian tissues. Two major calpains have been identified; calpain I and calpain II. While calpain II is the predominant form in many tissues, calpain I is thought to be the predominant form in pathological conditions of nerve tissues. The calpain family of cysteine proteases has been implicated in many diseases and disorders, including neurodegeneration, stroke, Alzheimer's, amyotrophy, motor neuron damage, acute central nervous system injury, muscular dystrophy, bone resorption, platelet aggregation, cataracts and inflammation. Calpain I has been implicated in excitatory amino-acid induced neurotoxicity disorders including ischemia, hypoglycemia, Huntington's Disease, and epilepsy.

The lysosomal cysteine protease cathepsin B has been implicated in the following disorders: arthritis, inflammation, myocardial infarction, tumor metastasis, and muscular dystrophy. Other lysosomal cysteine proteases include cathepsins C, H, L and S. Interleukin-1 β converting enzyme ("ICE") is a cysteine protease which catalyzes the formation of interleukin-1 β . Interleukin-1 β is an immunoregulatory protein implicated in the following disorders: inflammation, diabetes, septic shock, rheumatoid arthritis, and Alzheimer's disease. ICE has also been linked to apoptotic cell death of neurons, which is implicated in a variety of neurodegenerative disorders including Parkinson's disease, ischemia, and amyotrophic lateral sclerosis (ALS).

Cysteine proteases are also produced by various pathogens. The cysteine protease clostripain is produced by *Clostridium histolyticum*. Other proteases are produced

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by *Trypanosoma cruzi*, malaria parasites *Plasmodium falciparum* and *P. vinckei* and *Streptococcus*. Hepatitis A viral protease HAV C3 is a cysteine protease essential for processing of picornavirus structural proteins and enzymes.

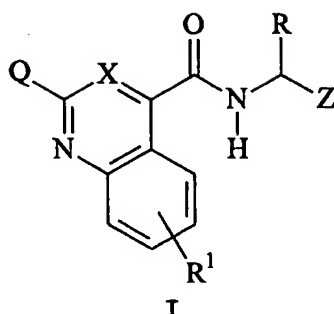
5 Exemplary serine proteases implicated in degenerative disorders include thrombin, human leukocyte elastase, pancreatic elastase, chymase and cathepsin G. Specifically, thrombin is produced in the blood coagulation cascade, cleaves fibrinogen to form fibrin and activates
10 Factor VIII; thrombin is implicated in thrombophlebitis, thrombosis and asthma. Human leukocyte elastase is implicated in tissue degenerative disorders such as rheumatoid arthritis, osteoarthritis, atherosclerosis, bronchitis, cystic fibrosis, and emphysema. Pancreatic
15 elastase is implicated in pancreatitis. Chymase, an enzyme important in angiotensin synthesis, is implicated in hypertension, myocardial infarction, and coronary heart disease. Cathepsin G is implicated in abnormal connective tissue degradation, particularly in the lung.

20 Given the link between cysteine and serine proteases and various debilitating disorders, compounds which inhibit these proteases would be useful and would provide an advance in both research and clinical medicine. The present invention is directed to these, as well as
25 other, important ends.

SUMMARY OF THE INVENTION

The present invention is directed to selected quinoline-containing α -ketoamide inhibitors of cysteine and serine proteases represented by the general Formula I:

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wherein:

X is CH, N, or CQ¹, with the proviso that when X
5 is CQ¹, at least one of Q or Q¹ is H;

R is selected from the group consisting of H,
alkyl having from one to about 6 carbons, arylalkyl having
from about 7 to about 15 carbons, heteroalkyl in which the
ring contains from about 5 to about 14 ring atoms,
10 heteroarylalkyl in which the heteroaryl ring contains from
about 5 to about 14 ring atoms, alkoxyalkyl, a side chain
of a naturally occurring amino acid in the R or S
configuration, and (CH₂)_nNH-L, said alkyl, arylalkyl,
heteroalkyl, and heteroarylalkyl groups being optionally
15 substituted with one or more J groups;

L is selected from the group consisting of
alkoxycarbonyl having from 2 to about 7 carbons,
arylalkoxycarbonyl in which the arylalkoxy group contains
about 7 to about 15 carbons, S(=O)₂R², and N-nitroimino;

20 R² is selected from the group consisting
of lower alkyl, and aryl having from about 6 to about 14
carbons;

R¹ is selected from the group consisting of H,
halogen, cyano, nitro, sulfonic acid, hydroxyl, alkyl,
25 alkoxy, hydroxymethyl, alkoxyethyl, arylalkyl, carboxyl,
alkoxycarbonyl, alkylcarbonyloxy, haloalkyl, N(RR³), and
acyl;

R³ is the same as R;

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Q is selected from the group consisting of H, lower alkyl, cycloalkyl, hydroxyl, alkoxy, halogen, arylalkyl having from about 7 to about 15 carbons, arylalkenyl having from about 8 to about 16 carbons, 5 arylalkynyl having from about 8 to about 16 carbons, aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, heteroalkyl having from about 5 to about 14 ring atoms, cycloalkyl having from about 3 to about 10 carbons, S-R, S(=O)R, S(=O)₂R, N(RR³), 10 and NHS(=O)₂R, said arylalkyl, arylalkenyl, arylalkynyl, aryl, heteroaryl, and heteroalkyl groups being optionally substituted with one or more J groups;

Q¹ is the same as Q;

Z is COCONH-R⁷;

15 R⁷ is selected from the group consisting of K, -A-N(R⁸)-G, -O-A-N(R⁸)-G, -A-SO₂N(R⁸)(R⁹), and -O-A-SO₂N(R⁸)(R⁹);

K is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, 20 heteroaryl, aryl, arylalkyl, heterocycloalkyl, alkoxy, alkoxyalkyl, arylalkyloxy, and N(RR³), said K groups being optionally substituted with one or more J groups;

A is lower alkylene optionally substituted with one or more J groups;

25 R⁸ is selected from the group consisting of H and lower alkyl;

R⁹ is selected from the group consisting of H, alkyl, aryl, and heterocyclyl, said alkyl, aryl, and heterocyclyl groups being optionally substituted with one 30 or more J groups;

G is selected from the group consisting of C(=O)aryl, C(=O)heteroaryl, C(=O)heteroalkyl, alkanoyl, C(=S)NH(aryl), C(=O)NH(aryl), C(=O)NH(cycloalkyl), CO₂ - (aryl), C(=O)alkyl, CO₂(alkyl), CO₂(arylalkyl),

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alkylsulfonyl, alkenylsulfonyl, arylsulfonyl, heteroarylsulfonyl, a side chain of a naturally occurring amino acid in the R or S configuration, a blocking group, and $\text{SO}_2\text{N}(\text{RR}^3)$, said G groups being optionally substituted
5 with one or more J groups;

J is selected from the group consisting of H, halogen, cyano, nitro, hydroxyl, alkyl, alkoxy, aryl, arylalkyl, alkoxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, haloalkyl, aminoalkyl, haloalkoxy,
10 $\text{SO}_2\text{N}(\text{RR}^3)$, $\text{SO}_2\text{NH}(\text{aryl})$, $\text{SO}_2\text{NH}(\text{heteroaryl})$, $\text{NHC}(=\text{O})\text{NH}(\text{aryl})$, $\text{NH}(\text{C}=\text{O})\text{NH}(\text{heteroaryl})$, $\text{NHSO}_2(\text{aryl})$, $\text{NHC}(=\text{O})\text{alkyl}$, $\text{NHC}(=\text{O})\text{aryl}$, $\text{NHC}(=\text{O})\text{heteroaryl}$, $\text{N}(\text{RR}^3)$, and $\text{NH}=\text{C}(\text{NH}_2)_2$;

n is an integer from 2 to 6;

or a pharmaceutically acceptable salt thereof;

15 with the proviso that when R^7 is K, then Q is selected from the group consisting of optionally substituted arylalkenyl and optionally substituted arylalkynyl; and

with the further proviso that when K is alkyl,
20 then X is not CH when Q is optionally substituted arylalkynyl.

In some preferred embodiments of the compounds of Formula I, X is CH. In further preferred embodiments of the compounds of Formula I, R is selected from the group
25 consisting of alkyl having from 2 to 4 carbons, and arylalkyl, with benzyl being particularly preferred.

In some preferred embodiments of the compounds of Formula I, R^1 is H or alkoxy, with H being preferred.

In some preferred embodiments of the compounds of Formula I, Q is selected from the group consisting of
30 arylalkynyl, aryl and halo, with phenylalkynyl being preferred.

In further preferred embodiments of the compounds of Formula I, A is selected from the group consisting of

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$(CH_2)_n$ wherein n is 2 or 3, and $(CH_2)_vCH_2-J$ where v is an integer from 1 to 6. When A is $(CH_2)_vCH_2-J$, v is preferably 2 or 3.

In some preferred embodiments of the compounds of Formula I, K is selected from the group consisting of alkyl, hydroxyalkyl, haloalkyl, alkynyl, heterocycloalkyl, arylalkyl, and heteroalkyl.

In further preferred embodiments of the compounds of Formula I, G is selected from the group consisting of substituted or unsubstituted $C(=O)aryl$, $C(=O)heteroaryl$, arylsulfonyl, and heteroarylsulfonyl. Preferably, G is selected from the group consisting of unsubstituted arylsulfonyl, substituted arylsulfonyl, unsubstituted heteroarylsulfonyl and substituted heteroarylsulfonyl.

In some preferred embodiments of the compounds of Formula I, X is CH , Z is $COCONH-K$, R_1 is H , and R is selected from the group consisting of alkyl having from 2 to 4 carbons and arylalkyl, with benzyl being preferred.

In some especially preferred embodiments of the compounds of Formula I, X is CH , Z is $COCONH-K$, R_1 is H , R is selected from the group consisting of alkyl having from 2 to 4 carbons and arylalkyl, with benzyl being preferred, and Q is arylalkynyl, with phenylethynyl being preferred.

In some especially preferred embodiments of the compounds of Formula I, Q , X , R^1 , R , and Z are selected from the group of substituents listed in Tables 2 to 5, *infra*. Particularly preferred embodiments of the compounds of Formula I are listed in Tables 2 to 5, *infra*.

Because the quinoline-containing α -ketoamides of the invention inhibit cysteine proteases and serine proteases, they can be used in both research and therapeutic settings.

In a research environment, preferred compounds having defined attributes can be used to screen for natural

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and synthetic compounds which evidence similar characteristics in inhibiting protease activity. The compounds can also be used in the refinement of *in vitro* and *in vivo* models for determining the effects of
5 inhibition of particular proteases on particular cell types or biological conditions.

In a therapeutic setting, given the connection between cysteine proteases and certain defined disorders, and serine proteases and certain defined disorders,
10 compounds of the invention can be utilized to alleviate, mediate, reduce and/or prevent disorders which are associated with abnormal and/or aberrant activity of cysteine proteases and/or serine proteases.

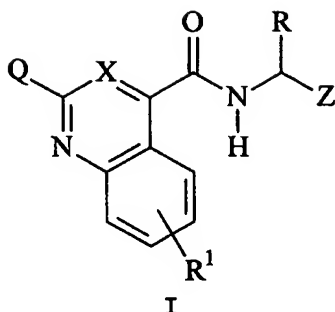
In preferred embodiments, compositions are
15 provided for inhibiting a serine protease or a cysteine protease comprising a compound of the invention. In other preferred embodiments, methods are provided for inhibiting serine proteases or cysteine proteases comprising contacting a protease selected from the group consisting of
20 serine proteases and cysteine proteases with an inhibitory amount of a compound of the invention.

Methodologies for making the present quinoline-containing α -ketoamide inhibitors are also disclosed. Other useful methodologies will be apparent to those
25 skilled in the art, once armed with the present disclosure. These and other features of the compounds of the subject invention are set forth in more detail below.

DETAILED DESCRIPTION

Disclosed herein are selected quinoline-
30 containing α -ketoamide serine and cysteine protease inhibitors, which are represented by the following Formula I:

- 9 -



wherein:

X is CH, N, or CQ¹, with the proviso that when X
5 is CQ¹, at least one of Q or Q¹ is H;

R is selected from the group consisting of H,
alkyl having from one to about 6 carbons, arylalkyl having
from about 7 to about 15 carbons, heteroalkyl in which the
ring contains from about 5 to about 14 ring atoms,
10 heteroarylalkyl in which the heteroaryl ring contains from
about 5 to about 14 ring atoms, alkoxyalkyl, a side chain
of a naturally occurring amino acid in the R or S
configuration, and (CH₂)_nNH-L, said alkyl, arylalkyl,
heteroalkyl, and heteroarylalkyl groups being optionally
15 substituted with one or more J groups;

L is selected from the group consisting of
alkoxycarbonyl having from 2 to about 7 carbons,
arylalkoxycarbonyl in which the arylalkoxy group contains
about 7 to about 15 carbons, S(=O)₂R², and N-nitroimino;
20 R² is selected from the group consisting
of lower alkyl, and aryl having from about 6 to about 14
carbons;

R¹ is selected from the group consisting of H,
halogen, cyano, nitro, sulfonic acid, hydroxyl, alkyl,
25 alkoxy, hydroxymethyl, alkoxymethyl, arylalkyl, carboxyl,
alkoxycarbonyl, alkylcarbonyloxy, haloalkyl, N(RR³), and
acyl;

R³ is the same as R;

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Q is selected from the group consisting of H, lower alkyl, cycloalkyl, hydroxyl, alkoxy, halogen, arylalkyl having from about 7 to about 15 carbons, arylalkenyl having from about 8 to about 16 carbons, 5 arylalkynyl having from about 8 to about 16 carbons, aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, heteroalkyl having from about 5 to about 14 ring atoms, cycloalkyl having from about 3 to about 10 carbons, S-R, S(=O)R, S(=O)₂R, N(RR³), 10 and NHS(=O)₂R, said arylalkyl, arylalkenyl, arylalkynyl, aryl, heteroaryl, and heteroalkyl groups being optionally substituted with one or more J groups;

Q¹ is the same as Q;

Z is COCONH-R⁷;

15 R⁷ is selected from the group consisting of K, -A-N(R⁸)-G, -O-A-N(R⁸)-G, A-SO₂N(R⁸)(R⁹), and -O-A-SO₂N(R⁸)(R⁹);

K is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, 20 heteroaryl, aryl, arylalkyl, heterocycloalkyl, alkoxy, alkoxyalkyl, arylalkyloxy, and N(RR³), said K groups being optionally substituted with one or more J groups;

A is lower alkylene optionally substituted with one or more J groups;

25 R⁸ is selected from the group consisting of H and lower alkyl;

R⁹ is selected from the group consisting of H, alkyl, aryl, and heterocyclyl, said alkyl, aryl, and heterocyclyl groups being optionally substituted with one 30 or more J groups;

G is selected from the group consisting of C(=O)aryl, C(=O)heteroaryl, C(=O)heteroalkyl, alkanoyl, C(=S)NH(aryl), C(=O)NH(aryl), C(=O)NH(cycloalkyl),

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CO₂(aryl), C(=O)alkyl, CO₂(alkyl), CO₂(arylalkyl),
alkylsulfonyl, alkenylsulfonyl, arylsulfonyl,
heteroarylsulfonyl, a side chain of a naturally occurring
amino acid in the R or S configuration, a blocking group,
5 and SO₂N(RR³), said G groups being optionally substituted
with one or more J groups;

J is selected from the group consisting of H,
halogen, cyano, nitro, hydroxyl, alkyl, alkoxy, aryl,
arylalkyl, alkoxycarbonyl, alkylcarbonyloxy,
10 alkenylcarbonyloxy, haloalkyl, aminoalkyl, haloalkoxy,
SO₂N(RR³), SO₂NH(aryl) SO₂NH(heteroaryl), NHC(=O)NH(aryl),
NH(C=O)NH(heteroaryl), NHSO₂(aryl), NHC(=O)alkyl,
NHC(=O)aryl, NHC(=O)heteroaryl, N(RR³), and NH=C(NH₂)₂;

n is an integer from 2 to 6;

15 or a pharmaceutically acceptable salt thereof;

with the proviso that when R⁷ is K, then Q is
selected from the group consisting of optionally
substituted arylalkenyl and optionally substituted
arylalkynyl; and

20 with the further proviso that when K is alkyl,
then X is not CH when Q is optionally substituted
arylalkynyl.

It is recognized that various stereoisomeric
forms of the compounds of Formula I may exist. Preferred
25 compounds of the invention have the L-configuration at the
carbon to which the substituent R is attached. However,
racemates and individual enantiomers and mixtures thereof
form part of the present invention.

As used herein, the term "quinoline" denotes a
30 "quinoline" or a "quinoline N-oxide" structure.

In the compounds of Formula I, where a bond to a
substituent is shown to cross the bond connecting two atoms
in a ring, it is intended that such substituent may be
bound to any atom in the ring.

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As used herein, the term "alkyl" includes straight-chain, branched and cyclic hydrocarbon groups such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-ethylpentyl, 5 hexyl, octyl, cyclopropyl, methylcyclopentyl, cyclohexyl, and adamantane groups. Preferred alkyl groups have 1 to about 10 carbon atoms, with 1 to about 6 carbon atoms (i.e., "lower alkyl") being preferred. "Lower alkylene" groups are branched or unbranched alkylene groups of 1 to 10 about 6 carbon atoms such as, for example, ethylene (-CH₂CH₂-), propylene, butylene, hexylene, 1-methylethylene, 2-methylethylene, and 2-methylpropylene. "Acyl" (i.e., "alkanoyl") groups are alkylcarbonyl groups. "Aryl" groups are aromatic cyclic compounds including but not limited to 15 phenyl, tolyl, naphthyl, anthracyl, phenanthryl, pyrenyl, biphenyl, and xylyl. Preferred aryl groups include phenyl and naphthyl. The term "carbocyclic", as used herein, refers to cyclic groups in which the ring portion is composed solely of carbon atoms. The term "halogen" refers 20 to F, Cl, Br, and I atoms. The term "arylalkyl" (or "aralkyl") denotes alkyl groups which bear aryl groups, for example, benzyl groups.

As used herein, "alkoxy" groups are alkyl groups linked through an oxygen atom. Examples of alkoxy groups 25 include methoxy (-OCH₃) and ethoxy (-OCH₂CH₃) groups. In general, the term "oxy" when used as a suffix denotes attachment through an oxygen atom. Thus, alkoxycarbonyl groups are carbonyl groups which contain an alkoxy substituent, i.e., groups of general formula -C(=O)-O-R, 30 where R is alkyl. The term "alkoxyalkyl" denotes an alkoxy group attached to an alkyl group. The term "aryloxy" denotes an aryl group linked through an oxygen atom, and the term "arylalkyloxy" denotes an arylalkyl group linked through an oxygen atom.

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As used herein, the term "alkenyl" is intended to include straight-chain or branched hydrocarbon chains having at least one carbon-carbon double bond. Examples of alkenyl groups include ethenyl and propenyl groups.

5 Arylalkenyl groups are alkenyl groups that have one or more aryl groups appended thereto. As used herein, the term "alkynyl" is intended to include straight-chain or branched hydrocarbon chains having at least one carbon-carbon triple bond. Examples of alkynyl groups include ethynyl and
10 propynyl groups. Arylalkynyl groups are alkynyl groups that have one or more aryl groups appended thereto.

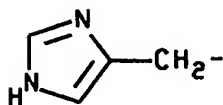
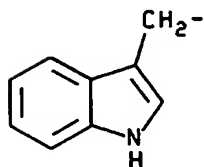
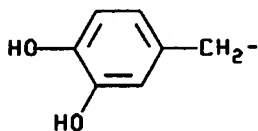
The terms "heterocycle", "heterocyclyl", and "heterocyclic" refer to cyclic groups in which a ring portion includes at least one heteroatom such as O, N or S.
15 Heterocyclic groups include "heteroaryl" as well as "heteroalkyl" groups. Preferred "heteroaryl" groups include pyridyl, pyrimidyl, pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, tetrazolyl, quinolyl, isoquinolyl, benzimidazolyl, thiazolyl, bipyridyl, phthalimido, and
20 benzothiazolyl. The term "heterocycloalkyl" denotes a heterocycle attached through a lower alkyl group. The term "heteroaryl" denotes aryl groups having one or more hetero atoms contained within an aromatic ring. The term "heteroarylalkyl" denotes a heteroaryl group attached
25 through an alkyl group. The term "heteroalkyl" denotes a heterocyclic group which contains at least one saturated carbon atom in the heterocyclic ring. Examples of heteroalkyl groups include piperidine, dihydropyridine, tetrahydroisoquinyl, and ϵ -caprolactam groups.

30 As used herein, the term "amino acid" denotes a molecule containing both an amino group and a carboxyl group. As used herein the term "L-amino acid" denotes an α -amino acid having the L- configuration around the α -carbon, that is, a carboxylic acid of general formula

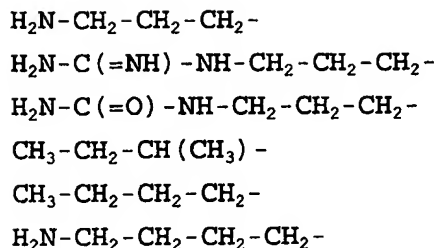
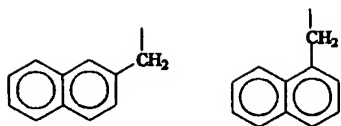
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CH(COOH)(NH₂)-(side chain), having the L-configuration. The term "D-amino acid" similarly denotes a carboxylic acid of general formula CH(COOH)(NH₂)-(side chain), having the D-configuration around the α-carbon. Side chains of L-amino acids include naturally occurring and non-naturally occurring moieties. Nonnaturally occurring (i.e., unnatural) amino acid side chains are moieties that are used in place of naturally occurring amino acid sidechains in, for example, amino acid analogs. See, for example, 10 Lehninger, *Biochemistry*, Second Edition, Worth Publishers, Inc, 1975, pages 73-75. One representative amino acid side chain is the lysyl side chain, -(CH₂)₄-NH₂. Other representative α-amino acid side chains are shown below in Table 1.

15

Table 1CH₃-HO-CH₂-C₆H₅-CH₂-HO-C₆H₄-CH₂-HS-CH₂-HO₂C-CH(NH₂)-CH₂-S-S-CH₂-CH₃-CH₂-CH₃-S-CH₂-CH₂-CH₃-CH₂-S-CH₂-CH₂-HO-CH₂-CH₂-CH₃-CH(OH)-HO₂C-CH₂-NHC(=O)-CH₂-HO₂C-CH₂-CH₂-NH₂C(=O)-CH₂-CH₂-(CH₃)₂-CH-(CH₃)₂-CH-CH₂-CH₃-CH₂-CH₂-

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Functional groups present in the compounds of Formula I may contain blocking groups. Blocking groups are known per se as chemical functional groups that can be selectively appended to functionalities, such as hydroxyl groups, amino groups, thio groups, and carboxyl groups. Protecting groups are blocking groups which can be readily removed from functionalities. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. Examples of such protecting groups are the benzyloxycarbonyl (Cbz; Z), toluenesulfonyl, t-butoxycarbonyl, methyl ester, and benzyl ether groups. Other preferred protecting groups according to the invention may be found in Greene, T.W. and Wuts, P.G.M., *"Protective Groups in Organic Synthesis"* 2d. Ed., Wiley & Sons, 1991.

Further blocking groups useful in the compounds of the present invention include those that bear acyl, aroyl, alkyl, alkanesulfonyl, arylalkanesulfonyl, or arylsulfonyl substituents on their amino groups. Other useful blocking groups include alkyl ethers, e.g., the methyl ether of serine.

The disclosed compounds of the invention are useful for the inhibition of cysteine proteases and serine proteases. As used herein, the terms "inhibit" and "inhibition" mean having an adverse effect on enzymatic activity. An inhibitory amount is an amount of a compound

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of the invention effective to inhibit a cysteine and/or serine protease.

Pharmaceutically acceptable salts of the cysteine and serine protease inhibitors also fall within the scope of the compounds as disclosed herein. The term "pharmaceutically acceptable salts" as used herein means an inorganic acid addition salt such as hydrochloride, sulfate, and phosphate, or an organic acid addition salt such as acetate, maleate, fumarate, tartrate, and citrate. Examples of pharmaceutically acceptable metal salts are alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt. Examples of pharmaceutically acceptable organic amine addition salts are salts with morpholine and piperidine. Examples of pharmaceutically acceptable amino acid addition salts are salts with lysine, glycine, and phenylalanine.

Compounds provided herein can be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable excipients and carriers. As noted above, such compositions may be prepared for use in parenteral administration, particularly in the form of liquid solutions or suspensions; or oral administration, particularly in the form of tablets or capsules; or intranasally, particularly in the form of powders, nasal drops, or aerosols; or dermally, via, for example, transdermal patches; or prepared in other suitable fashions for these and other forms of administration as will be apparent to those skilled in the art.

The composition may conveniently be administered in unit dosage form and may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980). Formulations for parenteral

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administration may contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils and vegetable origin, hydrogenated naphthalenes and the like. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be useful excipients to control the release of the active compounds. Other potentially useful parenteral delivery systems for these active compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, cyclodextrins and liposomes. Formulations for inhalation administration contain as excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration may also include glycocholate for buccal administration, a salicylate for rectal administration, or citric acid for vaginal administration. Formulations for transdermal patches are preferably lipophilic emulsions.

The materials for this invention can be employed as the sole active agent in a pharmaceutical or can be used in combination with other active ingredients which could facilitate inhibition of cysteine and serine proteases in diseases or disorders.

The concentrations of the compounds described herein in a therapeutic composition will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (e.g., hydrophobicity) of the compounds employed, and the route of administration. In general terms, the compounds of this invention may be provided in effective inhibitory amounts in an aqueous physiological buffer solution containing

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about 0.1 to 10% w/v compound for parenteral administration. Typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.01 mg/kg to 100 mg/kg of body weight per day. Such formulations typically provide inhibitory amounts of the compound of the invention. The preferred dosage of drug to be administered is likely, however, to depend on such variables as the type or extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of administration.

As used herein, the term "contacting" means directly or indirectly causing at least two moieties to come into physical association with each other. Contacting thus includes physical acts such as placing the moieties together in a container, or administering moieties to a patient. Thus, for example administering a compound of the invention to a human patient evidencing a disease or disorder associated with abnormal and/or aberrant activity of such proteases falls within the scope of the definition of the term "contacting".

The invention is further illustrated by way of the following examples which are intended to elucidate the invention. These examples are not intended, nor are they to be construed, as limiting the scope of the disclosure.

Examples

Examples 1-158:

The compounds shown in Tables 2 through 5 were prepared using conditions described in the "General Methods" section below. Enzyme inhibitory activity (IC_{50}) was determined as described in Examples 159 and 160.

In all Examples, R^1 is H unless otherwise noted.

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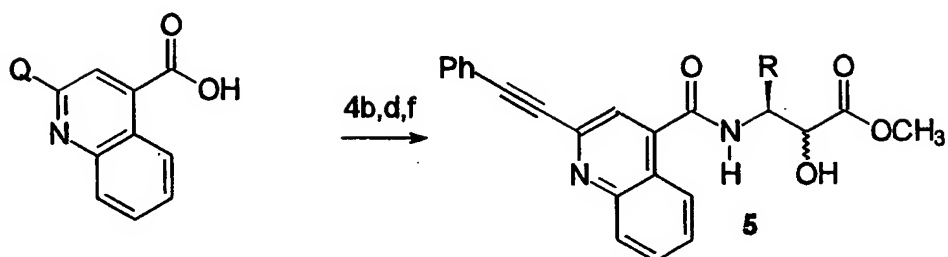
General Methods:

Thin layer chromatography was performed using silica gel coated plates (MK6F 60A, size 1 x 3 in, layer thickness 250 μ m, Whatman Inc.). Preparative thin layer chromatography was performed using silica gel coated plates (size 20 x 20 in, layer thickness 1000 micron, Analtech). Preparative column chromatography was carried out using Merck silica gel, 40-63 μ m, 230-400 mesh. ^1H NMR spectra were recorded on a GE QE300 Plus spectrometer at 300 MHz using tetramethylsilane as internal standard. Electrospray mass spectra were recorded on a VG platform II instrument (Fisons Instruments).

Compounds were prepared following one of the general methods A, B, C or D.

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General Method A

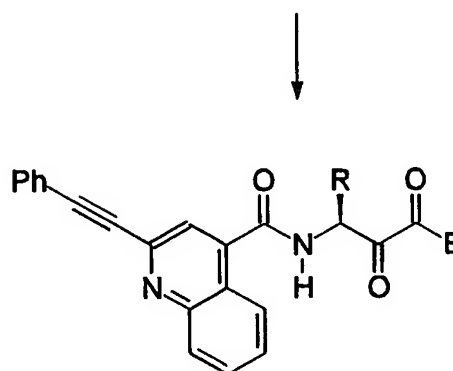


1 Q = OH

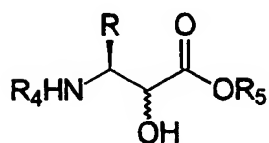
2 Q = Cl

3 Q = \equiv Ph

15 Q = CH=CHPh

16 Q = CH₂CH₂Ph6: B = OCH₃

7: B = OH

8: B = NHR₆H₂NR₆4a R₄ = tBOC, R₅ = H, R = CH₂Ph4b R₄ = H.HCl, R₅ = CH₃, R = CH₂Ph4c R₄ = tBOC, R₅ = H, R = C₄H₉4d R₄ = H.HCl, R₅ = CH₃, R = C₄H₉4e R₄ = tBOC, R₅ = H, R = C₃H₇4f R₄ = H.HCl, R₅ = CH₃, R = C₃H₇

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Preparation of Compound 2

A mixture of compound of formula 1 (20 g, 0.106 mol) and phosphorous oxychloride (50 mL, 0.54 mol) was held at reflux for 3 hours. After cooling, the reaction mixture was slowly poured into ice-water and a white precipitate was formed. The precipitate was filtered, thoroughly washed with cold water, and redissolved in ethyl acetate (300 mL). The solution was dried over anhydrous sodium sulfate. Filtration and solvent removal gave 14.78 g of compound 2 which was used without further purification.

Compound 2: tan solid; $^1\text{H-NMR}$ (DMSO-d_6) δ 8.60 (d, 1H), 8.00 (d, 1H), 7.90 (s, 1H), 7.80 (t, 1H), 7.70 (t, 1H). MS m/e 208 and 210 (M+H with isotopes of chlorine).

Preparation of Compound 3

A mixture of compound 2 (20 g, 0.0966 mol), phenylacetylene (13.02 g, 14 mL, 0.127 mol), $(\text{PPh}_3)\text{PdCl}_2$ (1.40 g, 0.00193 mol), CuI (0.42 g, 0.00386 mol), triethylamine (19.66 g, 27 mL, 0.192 mol) and anhydrous DMSO (150 mL) was heated at 60-70 °C for 3 hours. After cooling, the reaction mixture was slowly poured into ice-water (300 mL). The aqueous solution was acidified with 2 N HCl and extracted into methylene chloride (3 x 700 mL). The organic layer was washed with brine (1 x 250 mL), dried (anhydrous sodium sulfate) and concentrated to give a residue which, on recrystallization from methylene chloride-hexanes, yielded 23.8 g of compound 3.

Compound 3: white solid; $^1\text{H-NMR}$ (DMSO-d_6) δ 8.60 (d, 1H), 8.10 (d, 1H), 8.05 (s, 1H), 7.85 (t, 1H), 7.70 (m, 3H), 7.45 (m, 3H). MS m/e 274 (M+H).

30 Preparation of Compound 4a

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Compound 4a, and related hydroxy-acids used in this study, were synthesized following a general procedure of Harbeson et al., *J. Med. Chem.* 1994, 37, 2918-2929.

Preparation of Compound 4b

5 To a cooled (-10 °C) solution of compound 4a (4.30 g, 0.015 mol) in anhydrous methanol (50 mL) was added slowly thionyl chloride (3.20 mL). After 0.5 hour, the cooling bath was removed, the mixture was stirred for an additional 16 hours and concentrated to give a residue. Trituration
10 with ethyl acetate (30 mL) gave a white solid. The solid was separated by filtration and dried to give 3.50 g of compound 4b which was used directly in the next step; MS m/e 210(M+H).

15 Preparation of Compound 5 (R=Benzyl)

To a cooled (0 °C) solution of compound 3 (0.88 g, 0.0032 mol) in anhydrous DMF (10 mL) was added N-methylmorpholine (0.98 g, 0.0096 mol) followed by 1-HOBt (0.43 g, 0.0032 mol) and BOP (1.70 g, 0.0039 mol). The
20 mixture was stirred for 15 minutes and to it was added compound 4b (0.95 g, 0.0039 mol). The cooling bath was removed and the mixture was stirred for 4 hours, poured into ice-water (40 mL) and extracted into ethyl acetate (3 x 40 mL). The organic layer was washed with 2% citric acid
25 solution (2 x 40 mL), 2% sodium bicarbonate solution (2 x 40 mL), brine (1 x 50 mL) and dried over anhydrous sodium sulfate. Solvent evaporation under reduced pressure gave a crude material which was purified by flash column chromatography (eluant: 40% ethyl acetate in hexanes) to
30 produce 1.10 g of compound 5.

Compound 5 (Diastereomeric mixture): white solid; ¹H-NMR (CDCl₃) δ 8.10 (d, 1H), 7.80-7.20 (2 sets of m, 14H), 6.40 (2

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sets of d, 1H), 5.00 (m, 1H), 4.60 and 4.30 (2 sets of t, 1H), 3.85 and 3.75 (2 singlets, 3H), 3.50 and 3.35 (2 sets of d, 1H), 3.10 and 3.00 (2 sets of dd, 2H). MS m/e 465 (M+H).

5 Preparation of Compound 6 (R=Benzyl)

To a cooled (0 °C) solution of compound 5 (4.33 g, 9.33 mmol) in 1:1 anhydrous methylene chloride and anhydrous acetonitrile (60 mL) was slowly added Dess-Martin periodinane reagent (7.90 g, 18.66 mmol). The cooling bath
10 was removed and the mixture was stirred for an additional 2 hours. The mixture was then diluted with methylene chloride (50 mL) and washed with 10% sodium thiosulfate solution (5 x 50 mL), saturated sodium bicarbonate solution (2 x 50 mL), and brine (1 x 50 mL). Drying (anhydrous sodium sulfate)
15 and solvent removal under reduced pressure gave a residue which was purified by flash column chromatography (eluant: 1:1 EtOAc-hexanes) to yield 3.3 g of compound 6.

Compound 6: white solid; ¹H-NMR (CDCl₃) δ 8.20-7.20 (m, 15H), 6.65 (d, 1H), 5.80 (q, 1H), 3.95 (s, 3H), 3.50 (dd, 1H),
20 3.20 (dd, 1H). MS m/e 463 (M+H).

Preparation of Compound 7 (R=Benzyl)

A mixture of compound 6, (1.20 g, 2.60 mmol), 1 N NaOH (6.5 mL) and MeOH (15 mL) was stirred at room temperature for 1.5 hours. TLC (50% EtOAc in methylene chloride) showed
25 the complete disappearance of compound 6. The reaction mixture was concentrated at the rotavapor and redissolved in water (25 mL). The aqueous layer was washed with ether (2 x 15 mL) and acidified with 1 N HCl. The aqueous layer was then extracted into EtOAc (3 x 50 mL) and the combined ethyl
30 acetate layer was washed with brine (1 x 20 mL), dried (MgSO₄) and concentrated at the rotavapor to give 1.17 g of

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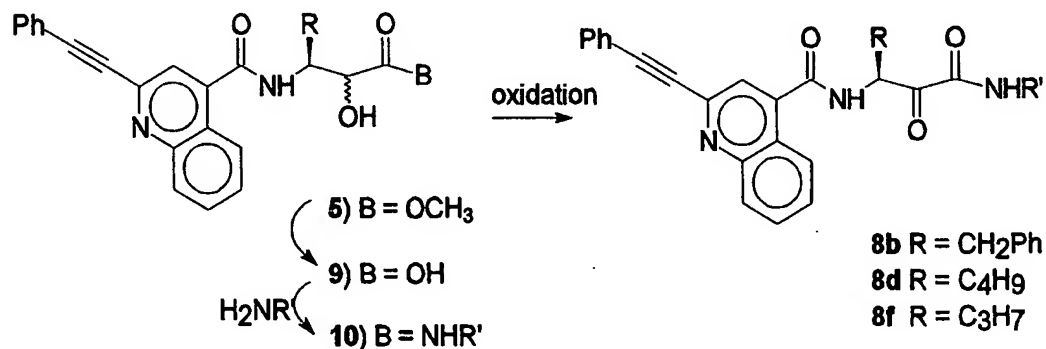
compound 7. $^1\text{H-NMR}$ (CDCl_3) of an aliquot showed absence of a COOCH_3 peak at δ 3.95; MS m/e 449 ($\text{M}+\text{H}$).

Preparation of Compound 8

5 Compound 8 was prepared, for example, by coupling compound 7 with an amine in the presence of NMM/HOBt/BOP/DMF, as described for the synthesis of compound 5. Purification was achieved by passing a solution of the crude material in methylene chloride or ethyl acetate
10 through Sep-Pak[®] Vac 6cc (1 g) silica cartridge (Waters Corporation, Milford, MA) and eluting with methylene chloride followed by mixtures of methylene chloride and ethyl acetate.

Harbeson et al. reported (*J. Med. Chem.* 1994, 37, 2918-
15 2929) that silica gel chromatography (of a ketoamide) epimerizes the chiral center at P_1 .

General Method B

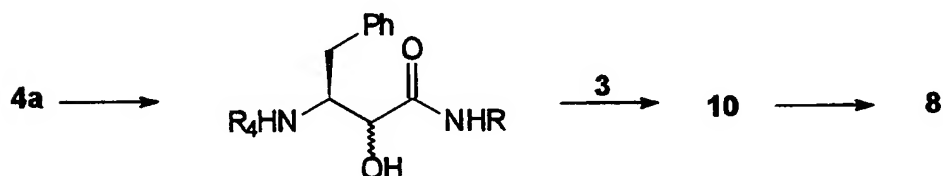


In General Method B, compounds of the formula 5 from General Method A were hydrolyzed to compounds of formula 9,
20 following the same procedure as described for the synthesis of compound 7. Compounds of formula 9 were then coupled with an amine (NMM/HOBt/BOP/DMF), as described for the

- 25 -

synthesis of compound 5, to produce the α -hydroxyamides (compound 10). Dess-Martin oxidation of compounds of formula 10 generated the ketoamides (compound 8) of the invention, which were used as such or recrystallized from organic solvents.

General Method C

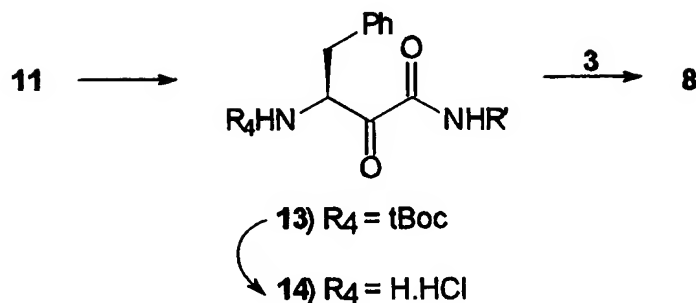


11) $R_4 = t\text{Boc}$

12) $R_4 = \text{H.HCl}$

In General Method C, compound 4a (General Method A) was initially coupled to an amine (NMM/HOBt/BOP/DMF), as described for the synthesis of compound 5, to generate compound 11. tBoc-deprotection was carried out under standard conditions (4 N HCl in dioxane, room temperature) to generate the amine salt, compound 12. Coupling of compound 12 with compound 3 (NMM/HOBt/BOP/DMF) as described for the synthesis of compound 5 produced compound 10. Dess-Martin oxidation of compound 10 generated compound 8.

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General Method D

In General Method D, compound 11 from General Method C was oxidized to generate compound 13, which on tBoc-deprotection generated compound 14. Coupling of compound 3 with compound 14 produced the ketoamide of the invention (compound 8).

It should be noted that although the General Methods A, B, C and D display only 2-phenylethynylquinoline (3) as the quinoline component of the invention, they are also valid for all other quinoline-4-carboxylic acids shown. Similarly, the methods are also valid for the different hydroxyacids derived from Leu, Nle (4c), Nva (4e), or by extension to any α -hydroxy- β -amino acid, in place of compound 4a (derived from phenylalanine).

15 Preparation of Intermediates

Preparation of Compounds 15 and 16.

Compound 3 (1.00 g, 3.66 mmol) was dissolved in DMF (14 mL), and the solution was stirred and hydrogenated at atmospheric pressure over 10% Pd-C (170 mg) for 50 hours (more 10% Pd-C (230 mg total) was added after 23 and 29 h). After filtration, the solvent was evaporated in vacuo at 40 °C. The residue was dissolved in methylene chloride, and the solution was rinsed twice with water and twice with brine,

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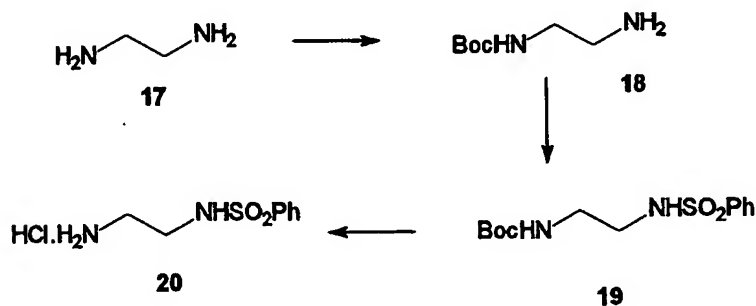
then dried over anhydrous MgSO_4 . Evaporation of the solvent afforded a crude mixture of compounds **15** and **16** (700 mg) as a brownish-orange semisolid. Compound **15** was purified by recrystallization from methanol. Compound **16** was purified from the resulting mother liquor by preparative TLC (eluent: CH_2Cl_2 - MeOH - HOAc, 94:5:1).

Compound **15**: MS m/e 276 ($M+H$).

Compound **16**: ^1H NMR ($\text{DMSO}-d_6$) δ 8.64 (d, 1H), 8.08 (d, 1H), 7.92 (s, 1H), 7.82 (t, 1H), 7.70 (t, 1H), 7.38 (m, 5H), 3.30 (t, 2H), 3.16 (t, 2H); MS m/e 278 ($M+H$).

The synthesis of a representative example of an amine containing a terminal sulfonamide moiety is shown in General Method E.

General Method E



15 Preparation of Compound **18**

To a solution of 1,2-ethylenediamine (compound **17**, 10.80 g, 12.00 mL, 0.18 mol) in THF (30 mL) was added slowly BOC-ON (22.10 g, 0.09 mol) in THF (70 mL) over a period of 4 hours. The reaction mixture was stirred overnight, concentrated on a rotavapor, and the residue was dissolved

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in water (150 mL). The aqueous layer was acidified (pH ~ 5-6) with solid citric acid monohydrate, washed with ether (3 x 50 mL), and then treated (at 0 °C) with 6 N NaOH solution to pH ~ 12-13. The basic solution was extracted into ethyl acetate (3 x 100 mL), and the combined ethyl acetate layer was dried (MgSO₄) and concentrated to generate 7.23 g of monoprotected diamine, compound 18.

Compound 18: semisolid; ¹H-NMR (CDCl₃) δ 5.00 (broad, 1H), 3.20 (broad q, 2H), 2.80 (t, 2H), 1.45 (s, 9H), 1.25 (broad, 2H).

Preparation of Compound 19

A cooled (0-5 °C) solution of the compound 18 (0.321 g, 0.002 mol) in methylene chloride (5 mL) was treated sequentially with triethylamine (0.243 g, 0.33 mL, 0.0024 mol) and benzenesulfonyl chloride (0.423 g, 0.30 mL, 0.0024 mol). The ice-bath was removed and the mixture was stirred for an additional 0.5 hour, washed successively with water (2 x 5 mL), cold (0-5 °C) 0.5 N HCl (1 x 5 mL), 2% NaHCO₃ solution (1 x 5 mL), and brine (1 x 5 mL). The solution was dried (MgSO₄), and the solvent was evaporated to give a residue which was washed several times with n-pentane to give 0.60 g of the sulfonamide derivative, compound 19.

Compound 19: white solid, mp 92-95 °C; R_f (TLC, 5% methanol in methylene chloride) 0.55; ¹H-NMR (CDCl₃) δ 7.85 (d, 2H), 7.55 (m, 3H), 5.30 (broad d, 1H), 4.85 (broad, 1H), 3.25 (broad q, 2H), 3.10 (broad q, 2H), 1.40 (s, 9H).

Preparation of Compound 20

A solution of compound 19 (0.560 g, 0.0019 mol) in 1,4-dioxane (4 mL) was treated with 4 N HCl in dioxane (4 mL). The mixture was stirred at room temperature for 1 hour and

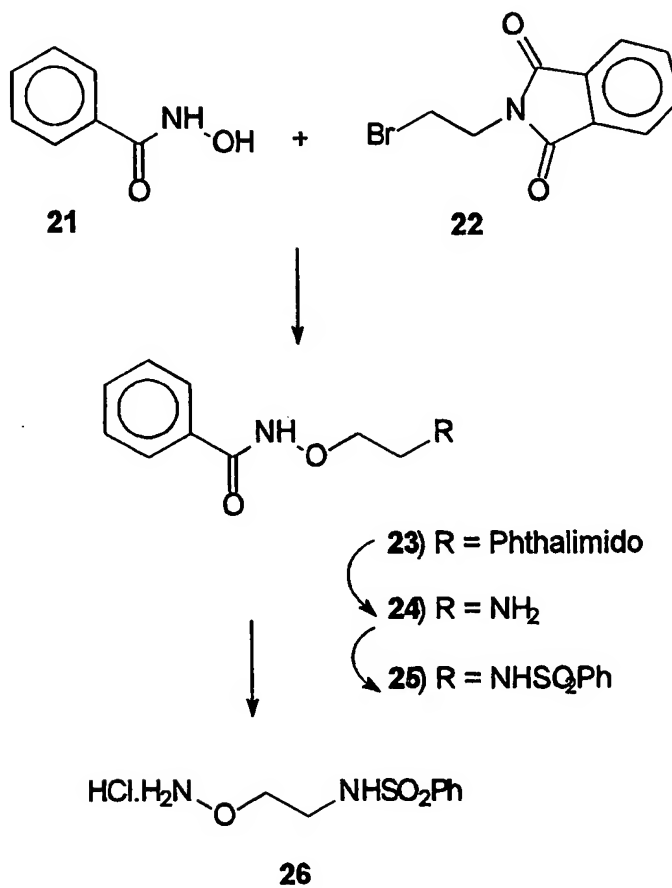
- 29 -

concentrated at the rotavapor. The residue was washed several times with ethyl acetate and dried under vacuum to give 0.40 g of the amine salt, compound 20.

Compound 20: white solid, mp 178-180 °C; ¹H-NMR (DMSO-d₆) δ
5 8.20-8.00 (broad t, 4H), 7.80 (d, 2H), 7.60 (m, 3H), 2.95 (broad q, 2H), 2.80 (broad, 2H).

The synthesis of a representative alkoxyamine, containing a terminal sulfonamide moiety, is shown in General Method F.

General Method F



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Preparation of Compound 23

To a solution of benzohydroxamic acid (compound 21, 5.00 g, 0.0365 mol) in DMF (50 mL) was slowly added sodium methoxide (2.50 g, 0.044 mol). The mixture was stirred for 5 10 minutes and to it was added N-(2-bromoethyl)phthalimide (compound 22, 9.00 g, 0.0333 mol). The reaction mixture was then stirred overnight, concentrated at the rotavapor, and partitioned between methylene chloride (200 mL) and 0.1 N NaOH (200 mL). The organic layer was separated, washed with 10 water (2 x 30 mL), dried (MgSO₄) and concentrated to a small volume. Trituration with ethanol produced 4.30 g of compound 23 which was used without further purification; MS *m/e* 311(M+H).

Preparation of Compound 24

15 A mixture of compound 23 (1.00 g, 0.0032 mol), hydrazine (1 mL) and 95% ethanol was held at reflux for 6 hours. After cooling, the reaction mixture was filtered and the filtrate was concentrated to give 0.575 g of compound 24 which was directly used in the next step; MS *m/e* 181(M+H).

20 Preparation of Compound 25

Compound 25 was generated from compound 24 following the same procedure as described for the synthesis of Compound 19 (General Method E); the crude product was purified by flash column chromatography (eluant 20% ethyl 25 acetate in methylene chloride) to give 0.75 g of compound 25; MS *m/e* 321(M+H).

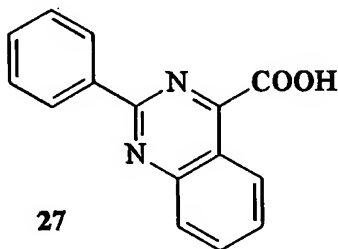
Preparation of Compound 26

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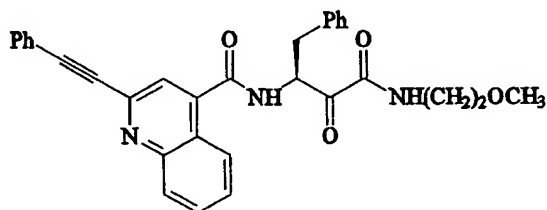
A mixture of compound 25 (0.60 g, 1.87 mmol) and 6 N HCl (20 mL) was held at reflux for 3 hours, cooled to room temperature and filtered. The filtrate was concentrated in vacuo overnight, to generate the amine salt, compound 26; MS
5 m/e 217 (M+H).

Preparation of Compound 27

2-Phenylquinazoline-4-carboxylic acid (compound 27) was prepared following a general procedure of Giardina et al, *J. Med. Chem.* **1997**, *40*, 1794-1807. This material can be
10 incorporated into General Method A replacing compound 3.



Preparation of the Compound of Example 11 by General Method A:



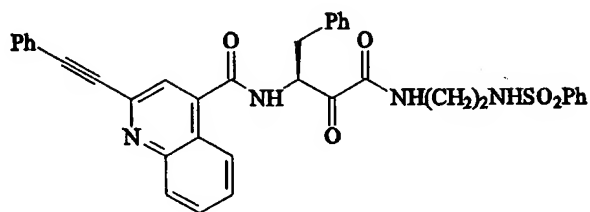
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17: pale yellow solid; $^1\text{H-NMR}$ (CDCl_3) δ 8.10 (d, 1H), 7.95 (d, 1H), 7.75 (t, 1H), 7.70-7.10 (a series of m, 13H), 6.55

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(d, 1H), 5.90 (m, 1H), 3.65-3.10 (a series of m, 6H), 3.40 (s, 3H). MS m/e 506(M+H).

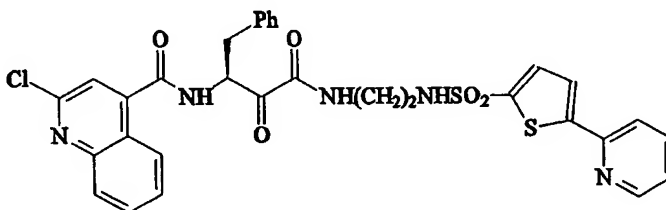
Preparation of the Compound of Example 96 by
General Method B:



5

105: pale yellow solid; $^1\text{H-NMR}$ (CDCl_3) δ 8.10 (d, 1H), 7.95 (d, 1H), 7.80-7.10 (a series of m, 19H), 6.55 (d, 1H), 5.90 (m, 1H), 5.10 (t, 1H), 3.50 (m, 3H), 3.20 (m, 3H). MS m/e
10 631(M+H).

Preparation of the Compound of Example 144 by
General Method C



15 159: pale yellow solid; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 9.35 (d, 1H), 8.90 (t, 1H), 8.50 (d, 1H), 8.10 (t, 1H), 8.00-7.70 (m, 7H), 7.55 (t, 2H), 7.40-7.10 (m, 6H), 5.50 (m, 1H), 3.30 (m, 2H), 3.00 (q, 3H), 2.75 (m, 1H). MS m/e 648 and 650(M+H, with

- 33 -

different isotopes of chlorine), 670 and 672 (M+Na, with different isotopes of chlorine).

Example 159

Inhibition of Cysteine Protease Activity

5 To evaluate inhibitory activity, stock solutions (40 times concentrated) of each compound to be tested were prepared in 100% anhydrous DMSO and 5 μ l of each inhibitor preparation was aliquoted into each of three wells of a 96-well plate. Recombinant human calpain I, prepared by the
10 method of Meyer et al. (*Biochem. J.* 1996, 314: 511-519), was diluted into assay buffer (i.e., 50mM Tris, 50mM NaCl, 1mM EDTA, 1mM EGTA, and 5mM β -mercaptoethanol, pH 7.5, including 0.2mM Succ-Leu-Tyr-MNA), and 175 μ l was aliquoted into the same wells containing the independent inhibitor stocks as
15 well as to positive control wells containing 5 μ l DMSO, but no compound. To start the reaction, 20 μ l of 50 mM CaCl_2 in assay buffer was added to all wells of the plate, excepting three, which were used as background signal baseline controls. Substrate hydrolysis was monitored every 5
20 minutes for a total of 30 minutes. Substrate hydrolysis in the absence of inhibitor was linear for up to 15 minutes.

Inhibition of calpain I activity was calculated as the percent decrease in the rate of substrate hydrolysis in the presence of inhibitor relative to the rate in its absence.
25 Comparison between the inhibited and control rates was made within the linear range for substrate hydrolysis. The IC_{50} s of inhibitors (concentration yielding 50% inhibition) were determined from the percent decrease in rates of substrate hydrolysis in the presence of five to seven different
30 concentrations of the test compound. The results were plotted as percent inhibition versus log inhibitor concentration, and the IC_{50} was calculated by fitting the data to the four-parameter logistic equation shown below ..

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using the program GraphPad Prism (GraphPad Software, Inc., San Diego, CA.).

$$y = d + [(a-d) / (1 + (x / c)^b)]$$

The parameters a, b, c, and d are defined as follows: a is % inhibition in the absence of inhibitor, b is the slope, c is the IC₅₀, and d is the % inhibition at an infinite concentration of inhibitor.

Results are presented Tables 2-5.

To demonstrate activity against another cysteine protease, cathepsin B (Calbiochem, cat#219364), assays were performed substantially the same as outlined above except that the cathepsin B was diluted into a different assay buffer consisting of 50mM sodium acetate (pH 6.0)/1mM EDTA/1mM dithiothreitol and the substrate used was 0.1mM Cbz-Phe-Arg-AMC (Bachem cat# I-1160). Additionally, the order of reagents added to the plate was altered because the enzyme is constitutively active. Following inhibitor addition to the plates, appropriate 2x concentrated stock dilutions of the enzyme preparations were made in assay buffer and 100µl added to each well. The assay was initiated by addition of 100µl of 2x concentrated stock dilution of substrate in assay buffer. Substrate hydrolysis was monitored using a Fluoriskan II (ex=390 nm; em=460 nm). Results are presented in Table 6.

25

Example 160

Inhibition of Serine Protease Activity

To demonstrate activity against the serine protease α-chymotrypsin (Sigma Chem. Co. Cat. #C-3142) the protocol of Example 159 was followed except that the enzyme was diluted into assay buffer consisting of 50mM Hepes (pH ..

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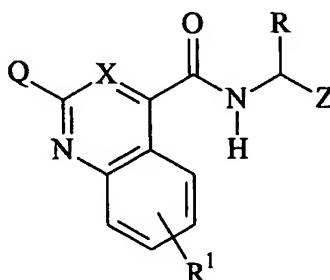
- 35 -

7.5)/0.5M NaCl and the final substrate concentration used was 0.03mM Succ-Ala-Ala-Pro-Phe-AMC (Bachem, Inc. Cat. #I-1465). Additionally, because α -chymotrypsin is not a calcium sensitive enzyme and is constitutively active,

5 following addition of inhibitor stocks to the 96 well plates, 100 μ l of a 2-fold concentrated stock of enzyme in dilution buffer was first added and the reaction was started by addition of 100 μ l of a 2-fold concentrated stock of substrate in assay buffer. Substrate hydrolysis was

10 monitored every 5 minutes up to 30 minutes using a Fluoroskan II (ex=390nm em=460nm). Results are listed in Table 6.

Table 2



Q = Phenylethynyl

X = CH

R = CH₂C₆H₅Z = COCONH-R⁷

Ex.	R ⁷	Calpain I IC ₅₀ nM**	Synth. Method	Mass Spectrum
				MH+
1	CH ₂ C≡CH	(91%)	A	486
2	CH ₂ CF ₃	(98%)	A	530
3	CH ₂ CH=CH ₂	210	A	488
4	CH ₂ cyclopropane	(100%)	A	502
5	CH ₂ CH ₂ CN	(95%)	A	501
6	CH ₂ CH ₂ cyclohexene-1-yl	(89%)	A	556
7	CH ₂ CH(OCH ₃) ₂	110	A	536

	8	$\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$	570	A	564
	9	$\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OC}_6\text{H}_{13}$	230	A	664
	10	$\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$	630	A	536
	11	$\text{CH}_2\text{CH}_2\text{OCH}_3$	480	A	506
5	12	$\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	(94%)	A	506
	13	$(\text{CH}_2)_4\text{OH}$	(100%)	A	520
	14	$(\text{CH}_2)_5\text{OH}$	(98%)	A	534
	15	adamantyl	(41%)	A	582
	16	cyclopropane	(100%)	A	488
10	17	(1-benzyl)piperidin-4-yl	638	A	621
	18	(2-methylcyclohexyl)	(76%)	A	544
	19	(4-methylcyclohexyl)	(91%)	A	544
	20	(3-methylcyclohexyl)	(94%)	A	544
	21	4-piperidine-1- CO_2Et	(100%)	A	603
15	22	ϵ -caprolactam	78	A	559
	23	$\text{CH}(\text{Bn})\text{CH}_2\text{OH}$	(75%)	A	582
	24	$\text{CH}(\text{CH}_2\text{OCH}_3)\text{CH}(\text{OH})\text{Ph}$	(21%)	A	582
	25	$\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2)_4\text{NHC}(\text{NHBoc})=\text{N Boc}$	(42%)	A	805
	26	$\text{CH}(\text{CH}_3)$ -1-Naphthyl	(31%)	A	602
20	27	$\text{CH}(\text{CH}_3)\text{Ph}$	510	A	552
	28	cyclohexan-2-ol	(61%)	A	546
	29	[trans]cyclohexan-4-ol	296	A	546
	30	cyclohexyl	(85%)	A	530
	31	cyclopentane-1- CH_2OH	(27%)	A	546
25	32	tetrahydronaphth-1-yl	(31%)	A	578
	33	piperon-5-yl	388	A	582
	34	$(\text{CH}_2)_4\text{Ph}$	227	A	580
	35	benzodioxan-6-yl	(71%)	A	582
	36	CH_2Ph	79*	B	538
30	37	$\text{CH}_2(3,4\text{-dimethoxy-Ph})$	(95%)	A	598
	38	$\text{CH}_2(3,5\text{-dimethoxy-Ph})$	(92%)	A	598
	39	$\text{CH}_2(4\text{-NH}_2\text{SO}_2\text{-Ph})$	184	A	617
	40	$\text{CH}_2\text{-C}_6\text{H}_4\text{-3-NO}_2$	(95%)	A	583
	41	$\text{CH}_2\text{CH}_2(3,4\text{-dimethoxy-Ph})$	(88%)	A	612
35	42	$\text{CH}_2\text{CH}_2(4\text{-NH}_2\text{SO}_2\text{-Ph})$	69	A	631
	43	$\text{CH}_2\text{CH}_2\text{Ph}$	390	A	552
	44	CH_2CHPh_2	(85%)	A	628
	45	$\text{CH}_2\text{-pyrid-2-yl}$	210	A	540
	46	$\text{CH}_2\text{-pyrid-3-yl}$	(91%)	A	540
40	47	$\text{CH}_2\text{-pyrid-4-yl}$	(98%)	A	540
	48	$\text{CH}_2\text{CH}_2\text{-2-methyl-5-NO}_2\text{-imidazole}$	(95%)	A	601

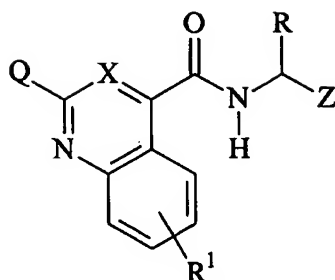
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5	49	CH ₂ CH ₂ -5-MeO-indole-3-yl	160	A	621
	50	CH ₂ CH ₂ CH ₂ -imidazol-1-yl	(84%)	A	556
	51	CH ₂ CH ₂ CH ₂ -morpholin-4-yl	424	A	575
	52	CH ₂ CH ₂ CH ₂ -pyrrolidin-2-one	366	A	573
	53	CH ₂ CH ₂ -Phthalimide	226	A	621
10	54	CH ₂ tetrahydrofuran-2-yl	(84%)	A	532
	55	indan-2-yl	(60%)	A	564
	56	CH ₂ CH ₂ NHCO (4-F-Ph)	146	A	613
	57	CH ₂ CH ₂ NHCO (4-MeOPh)	(71%)	A	625
	58	CH ₂ CH ₂ NHCO-2-furanyl	98	A	585
15	59	CH ₂ CH ₂ NHCO-morpholine	248	A	604
	60	CH ₂ CH ₂ NHCOCH ₃	140	A	533
	61	CH ₂ CH ₂ NHCONH (4-Br-Ph)	(94%)	A	689
	62	CH ₂ CH ₂ NHCONH (4-MeOPh)	190	A	640
	63	CH ₂ CH ₂ NHCONH-Adamant-1-yl	257	A	668
20	64	CH ₂ CH ₂ NHCONHPh	67	A	610
	65	CH ₂ CH ₂ NHCOPh	(100%)	A	595
	66	CH ₂ CH ₂ NHCSNH (4-MeOPh)	113	A	656
	67	CH ₂ CH ₂ NHCSNH (4-NO ₂ -Ph)	93	A	671
	68	CH ₂ CH ₂ NHSO ₂ (2-NO ₂ -Ph)	260	A	676
25	69	CH ₂ CH ₂ NHSO ₂ (4-F-Ph)	47	A	649
	70	CH ₂ CH ₂ NHSO ₂ - (1-methylimidazol-4-yl)	137	A	635
	71	CH ₂ CH ₂ NHSO ₂ - (2,1,3-thiadiazol-4-yl)	89	A	689
	72	CH ₂ CH ₂ NHSO ₂ - (2,5-dichloroPh)	(96%)	A	699
	73	CH ₂ CH ₂ NHSO ₂ - (2-MeO ₂ C-thiophene-3-yl)	220	A	695
30	74	CH ₂ CH ₂ NHSO ₂ - (2-NC-Ph)	132	A	656
	75	CH ₂ CH ₂ NHSO ₂ - (3,4-dichloro-Ph)	100	A	699
	76	CH ₂ CH ₂ NHSO ₂ - (3,5-dimethylisoxazol-4-yl)	(98%)	A	650
	77	CH ₂ CH ₂ NHSO ₂ - (3-NC-Ph)	77	A	656
	78	CH ₂ CH ₂ NHSO ₂ - (3-NO ₂ -Ph)	(88%)	A	676
35	79	CH ₂ CH ₂ NHSO ₂ - (4-acetamido-Ph)	43	A	688
	80	CH ₂ CH ₂ NHSO ₂ - (4-CF ₃ O-Ph)	200	A	694
	81	CH ₂ CH ₂ NHSO ₂ - (4-MeO-Ph)	62	A	661
	82	CH ₂ CH ₂ NHSO ₂ - (4-NC-Ph)	70	A	656
	83	CH ₂ CH ₂ NHSO ₂ - (4-NH ₂ -Ph)	70	A	646
	84	CH ₂ CH ₂ NHSO ₂ - (4-NO ₂ -Ph)	26	B	676
	85	CH ₂ CH ₂ NHSO ₂ - (5-(BzNHCH ₂) thiophen-2-yl)	48	A	770

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5	86	CH ₂ CH ₂ NHSO ₂ -[5-(2-pyridinyl)thiophen-2-yl]	31	A	712
	87	CH ₂ CH ₂ NHSO ₂ -(pyridin-3-yl)	56*	C	632
	99	CH ₂ CH ₂ NHSO ₂ -naphth-2-yl	41	A	681
	89	CH ₂ CH ₂ NHSO ₂ -Quinolin-8-yl	130	A	682
	90	CH ₂ CH ₂ NHSO ₂ -thiophene-2-yl	76	A	637
10	91	CH ₂ CH ₂ NHSO ₂ CH=CH-Ph	42	A	657
	92	CH ₂ CH ₂ NHSO ₂ CH ₂ Ph	94	A	645
	93	CH ₂ CH ₂ NHSO ₂ CH ₃	180	A	569
	94	CH ₂ CH ₂ NHSO ₂ NMe ₂	141	A	598
	95	CH ₂ CH ₂ NHSO ₂ Ph	43	A	631
15	96	CH ₂ CH ₂ NHSO ₂ Ph	29*	B	631
	97	(CH ₂) ₃ NHBoc	(100%)	A	605
	98	(CH ₂) ₃ NHCONHPh	126	A	624
	99	(CH ₂) ₃ NHSO ₂ Me	130	A	583
	100	(CH ₂) ₃ NHSO ₂ Ph	55	A	645
20	101	(CH ₂) ₆ NHSO ₂ (5-Cl-naphthalen-1-yl)	(84%)	A	771
	102	OCH ₃	82	A	538
	103	OCH ₂ CH ₃	65	A	492
	104	OBn	60	A	554
	105	OCH ₂ CH ₂ NHSO ₂ Ph	128	A	647
25	106	(CH ₂) ₄ CH(CO ₂ Me)NHBoc	(97%)	A	691
	107	CH ₂ CH ₂ CO ₂ tBu	(93%)	A	576
	108	CH ₂ CH ₂ NH-L-Pro-SO ₂ Ph	(94%)	A	728
	109	CH(Bn)CO ₂ Me	655	A	610
	110	NMe ₂	(43%)	A	491
	111	CH ₂ CH ₂ O-COC(=CH ₂)CH ₃	(95%)	A	560

Table 3



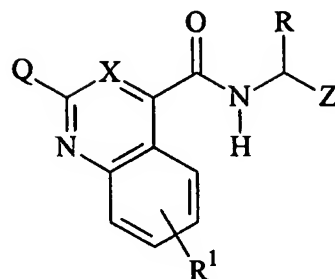
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Q = phenylethynyl
 X = CH
 Z = COCONH-R⁷

	Ex.	R ⁷	R	Calpain I IC ₅₀ nM**	Synth. Meth.	Mass Spect.
						MH+
10	112	CH ₂ CH ₂ OCH ₃	iBu	(95%)	B	472
	113	CH ₂ CH (OCH ₃) ₂	iBu	(92%)	A	502
	114	CH ₂ CH ₂ OCH ₂ CH ₂ OH	iBu	(93%)	A	502
	115	CH ₂ CH ₂ NHCO ₂ CH ₂ Ph	iBu	(100%)	B	591
	116	CH ₂ CH ₂ NHCONHPh	iBu	(89%)	A	576
15	117	CH ₂ CH ₂ NHSO ₂ Ph	iBu	(82%)	A	597
	118	CH ₂ CH ₂ NHSO ₂ (3, 4- Cl ₂ Ph)	iBu	120	B	666
	119	(CH ₂) ₃ NHSO ₂ Ph	iBu	(80%)	A	611
	120	CH ₂ CH ₂ OCH ₃	Et	(92%)	A	444
	121	CH ₂ CH (OCH ₃) ₂	Et	(94%)	A	474
20	122	CH ₂ CH ₂ NHSO ₂ Ph	Et	(89%)	A	569
	123	CH ₂ CH ₂ NHSO ₂ (3, 4- Cl ₂ Ph)	Et	58	A	637
	124	(CH ₂) ₃ NHSO ₂ Ph	Et	80	A	583
	125	CH ₂ CH ₂ NHCONHPh	Et	(32%)	A	548
	126	CH ₂ CH ₂ NHSO ₂ (3, 4- Cl ₂ Ph)	Bu	39	A	665
25	127	CH ₂ CH ₂ NHSO ₂ (4-NO ₂ Ph)	Bu	29	A	642
	128	CH ₂ CH ₂ NHSO ₂ (3, 4- Cl ₂ Ph)	Pr	187	A	651
	129	CH ₂ CH ₂ NHSO ₂ (4-NO ₂ Ph)	Pr	27	A	628

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Table 4



X = CH
 R = CH₂C₆H₅
 Z = COCONH-R⁷

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10

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20

Ex.	Q	R ⁷	Calpain I IC ₅₀ nM**	Synth Meth.	Mass Spec.
					MH+
130	PhCH=CH	Bu	105	D	506
131	H	CH ₂ CH ₂ NHSO ₂ Ph	(97%) *	C	531
132	H (N-oxide)	CH ₂ CH ₂ NHSO ₂ Ph	(96%)	D	547
133	HO	CH ₂ CH ₂ NHSO ₂ Ph	(95%)	D	547
134	CH ₃ O	CH ₂ CH ₂ NHSO ₂ Ph	(17%)	D	434
135	Piperidin- 1-yl	CH ₂ CH ₂ NHSO ₂ Ph	(91%)	D	624
136	Pyridin-3- yl	CH ₂ CH ₂ NHSO ₂ Ph	(99%)	D	608
137	PhCH ₂ CH ₂	CH ₂ CH ₂ NHSO ₂ Ph	116	D	635
138	Cl	CH ₂ CH ₂ NHSO ₂ Ph	28*	C	565
139	Cl	CH ₂ CH(CH ₃)NHSO ₂ Ph [S]	59	C	579
140	Cl	CH ₂ CH(CH ₃)NHSO ₂ Ph [R]	155	C	579
141	Cl	CH ₂ CH ₂ NHSO ₂ (Pyridi n-3-yl)	87*	C	566
142	CH ₃	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thiophen-2-yl]	24*	C	628
143	2-CH ₃ ***	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thiophen-2-yl]	35*	C	658
144	Cl	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thiophen-2-yl]	14	C	648

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145	Cyclo-propyl	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thiophen-2-yl]	71	C	654
146	Thiophen-2-yl	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thiophen-2-yl]	85	C	696
147	Cl	CH ₂ CH ₂ SO ₂ NHPh	81	C	565
148	Cl	CH ₂ CH ₂ SO ₂ NH (4-F-Ph)	75	C	583

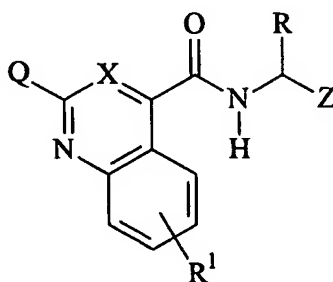
5 Footnotes to Tables 2-4:

* Single enantiomer

** (% inhibition of calpain I at 10,000 nM)

*** R¹ is 6-methoxy

Table 5

Z = COCONHR⁷

Ex	Q	X	R	R ⁷	Calpain I IC ₅₀ **	Synth Meth.	Mass Spec
149	Cl	CH	n-Bu	CH ₂ CH ₂ NHSO ₂ (4-NO ₂ Ph)	23	B	MH+ 576
150	Cl	CH	n-Pr	CH ₂ CH ₂ NHSO ₂ (4-NO ₂ Ph)	(78%)	B	562
151	Cl	CH	n-Bu	CH ₂ CH ₂ NHSO ₂ (3, 4-Cl ₂ Ph)	217	B	599
152	Cl	CH	n-Pr	CH ₂ CH ₂ NHSO ₂ (3, 4-Cl ₂ Ph)	325	B	585
153	Ph	N	Bn	CH ₂ CH ₂ NHSO ₂ Ph	(95%)	C	608

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	154	Ph	N	Bn	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thiophen-2-yl]	83	C	691
	155	Cl	CH	n-Bu	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thiophen-2-yl]	31	B	614
	156	Cl	CH	n-Pr	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thiophen-2-yl]	43	B	600
	157	Cl	CH	CH ₃ O- CH ₂	CH ₂ CH ₂ NHSO ₂ [5-(2-pyridinyl) thio-phen-2-yl]	61	B	603
5	158	Cl	CH	CH ₃ O- CH ₂	CH ₂ CH ₂ NHSO ₂ Ph	(94%)	B	519

** (% inhibition of calpain I at 10,000 nM)

Table 6: Inhibition of Cathepsin B and α -Chymotrypsin

	Cmpd. of Ex.	Cath. B IC ₅₀ (nM)	Chymotrypsin IC ₅₀ (nM)
10	100	360	36
	96	375	66
	103	435	380
	104	330	1160
	84	348	14
15	86	1030	475

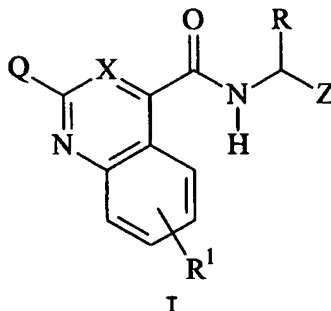
It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

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What is claimed is:

1. A compound having the Formula I:



5

wherein:

X is CH, N, or CQ¹, with the proviso that when X is CQ¹, at least one of Q or Q¹ is H;

R is selected from the group consisting of H, alkyl
 10 having from one to about 6 carbons, arylalkyl having from
 about 7 to about 15 carbons, heteroalkyl in which the ring
 contains from about 5 to about 14 ring atoms,
 heteroarylalkyl in which the heteroaryl ring contains from
 about 5 to about 14 ring atoms, alkoxyalkyl, a side chain
 15 of a naturally occurring amino acid in the R or S
 configuration, and (CH₂)_nNH-L, said alkyl, arylalkyl,
 heteroalkyl, and heteroarylalkyl groups being optionally
 substituted with one or more J groups;

L is selected from the group consisting of
 20 alkoxy carbonyl having from 2 to about 7 carbons,
 arylalkoxy carbonyl in which the arylalkoxy group contains
 about 7 to about 15 carbons, S(=O)₂R², and N-nitroimino;

R² is selected from the group consisting of
 lower alkyl, and aryl having from about 6 to about 14
 25 carbons;

R¹ is selected from the group consisting of H,
 halogen, cyano, nitro, sulfonic acid, hydroxyl, alkyl,
 alkoxy, hydroxymethyl, alkoxymethyl, arylalkyl, carboxyl,

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alkoxycarbonyl, alkylcarbonyloxy, haloalkyl, $N(RR^3)$, and acyl;

R^3 is the same as R;

Q is selected from the group consisting of H, lower
5 alkyl, cycloalkyl, hydroxyl, alkoxy, halogen, arylalkyl
having from about 7 to about 15 carbons, arylalkenyl having
from about 8 to about 16 carbons, arylalkynyl having from
about 8 to about 16 carbons, aryl having from about 6 to
about 14 carbons, heteroaryl having from about 5 to about
10 14 ring atoms, heteroalkyl having from about 5 to about 14
ring atoms, cycloalkyl having from about 3 to about 10
carbons, S-R, $S(=O)R$, $S(=O)_2R$, $N(RR^3)$, and $NHS(=O)_2R$, said
arylalkyl, arylalkenyl, arylalkynyl, aryl, heteroaryl, and
heteroalkyl groups being optionally substituted with one or
15 more J groups;

Q^1 is the same as Q;

Z is $COCONH-R^7$;

R^7 is selected from the group consisting of K, -
A- $N(R^8)-G$, -O-A- $N(R^8)-G$, -A- $SO_2N(R^8)(R^9)$, and
20 -O-A- $SO_2N(R^8)(R^9)$;

K is selected from the group consisting of alkyl,
alkenyl, alkynyl, cycloalkyl, heteroalkyl, heteroaryl,
aryl, arylalkyl, heterocycloalkyl, alkoxy, alkoxyalkyl,
arylalkyloxy, and $N(RR^3)$, said K groups being optionally
25 substituted with one or more J groups;

A is lower alkylene optionally substituted with
one or more J groups;

R^8 is selected from the group consisting of H and
lower alkyl;

30 R^9 is selected from the group consisting of H,
alkyl, aryl, and heterocyclyl, said alkyl, aryl, and
heterocyclyl groups being optionally substituted with one
or more J groups;

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- G is selected from the group consisting of C(=O)aryl, C(=O)heteroaryl, C(=O)heteroalkyl, alkanoyl, C(=S)NH(aryl), C(=O)NH(aryl), C(=O)NH(cycloalkyl), CO₂-(aryl), C(=O)alkyl, CO₂(alkyl), CO₂(arylalkyl),
5 alkylsulfonyl, alkenylsulfonyl, arylsulfonyl, heteroarylsulfonyl, a side chain of a naturally occurring amino acid in the R or S configuration, a blocking group, and SO₂N(RR³), said G groups being optionally substituted with one or more J groups;
- 10 J is selected from the group consisting of H, halogen, cyano, nitro, hydroxyl, alkyl, alkoxy, aryl, arylalkyl, alkoxy carbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, haloalkyl, aminoalkyl, haloalkoxy, SO₂N(RR³), SO₂NH(aryl), SO₂NH(heteroaryl), NHC(=O)NH(aryl), NH(C=O)NH(heteroaryl),
15 NHSO₂(aryl), NHC(=O)alkyl, NHC(=O)aryl, NHC(=O)heteroaryl, N(RR³), and NH=C(NH₂)₂;
n is an integer from 2 to 6;
or a pharmaceutically acceptable salt thereof;
with the proviso that when R⁷ is K, then Q is selected
20 from the group consisting of optionally substituted arylalkenyl and optionally substituted arylalkynyl; and
with the further proviso that when K is alkyl, then X is not CH when Q is optionally substituted arylalkynyl.
2. The compound of claim 1 wherein X is CH.
- 25 3. The compound of claim 1 wherein R is selected from the group consisting of alkyl having from 2 to 4 carbons, and arylalkyl.
4. The compound of claim 3 wherein R is benzyl.
5. The compound of claim 1 wherein R¹ is H or
30 alkoxy.

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6. The compound of claim 5 wherein R^1 is H.
7. The compound of claim 1 wherein Q is selected from the group consisting of arylalkynyl, aryl and halo.
- 5 8. The compound of claim 7 wherein Q is phenylalkynyl.
9. The compound of claim 1 wherein A is selected from the group consisting of $(CH_2)_n$ wherein n is 2 or 3, and $(CH_2)_vCH_2-J$ where v is an integer from 1 to 6.
- 10 10. The compound of claim 9 wherein A is $(CH_2)_vCH_2-J$, where v is 2 or 3.
11. The compound of claim 1 wherein K is selected from the group consisting of alkyl, hydroxyalkyl, haloalkyl, alkynyl, heterocycloalkyl, arylalkyl, and heteroalkyl.
- 15 12. The compound of claim 1 wherein G is selected from the group consisting of substituted or unsubstituted $C(=O)aryl$, $C(=O)heteroaryl$, arylsulfonyl, and heteroarylsulfonyl.
- 20 13. The compound of claim 12 wherein G is selected from the group consisting of unsubstituted arylsulfonyl, substituted arylsulfonyl, unsubstituted heteroarylsulfonyl and substituted heteroarylsulfonyl.
- 25 14. The compound of claim 1 wherein X is CH, Z is $COCONH-K$, R_1 is H, and R is selected from the group consisting of alkyl having from 2 to 4 carbons and arylalkyl.

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15. The compound of claim 14 wherein R is benzyl.

16. The compound of claim 1 wherein X is CH, Z is
COCONH-K, R₁ is H, R is selected from the group consisting
of alkyl having from 2 to 4 carbons and arylalkyl, and Q is
5 arylalkynyl.

17. The compound of claim 16 wherein R is benzyl.

18. The compound of claim 16 wherein Q is
phenylethynyl.

19. The compound of claim 1 wherein Q, X, R¹, R, and
10 Z are selected from the group of substituents listed in
Tables 2 to 5, *infra*.

20. The compound of Examples 1 through 158, as
described in Tables 2 through 5.

21. A composition for inhibiting a serine protease or
15 a cysteine protease comprising a compound of claim 1 and a
pharmaceutically acceptable carrier.

22. A method for inhibiting a serine protease or a
cysteine protease comprising contacting a protease selected
from the group consisting of serine proteases and cysteine
20 proteases with an inhibitory amount of a compound of claim
1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/21054

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/47, 31/445; C07D 215/12, 215/14, 215/20, 215/26

US CL :514/311, 314; 546/168, 170

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/311, 314; 546/168, 170

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS Text, CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr., Vol. 116, No. 25, 22 June 1992 (Columbus. OH, USA), page 838, column 2, the abstract No. 256040, TSUSHIMA, T. et al., 'Preparation of amino acid derivatives as digestive tract hormone antagonists.' Jpn. Kokai Tokkyo Koho. JP 03294253 A2, 25 December 1991.	1-22
Y	Chem. abstr., Vol 120. No.13, 28 March 1994 (Columbus. OH, USA), page 1236, column 2, the abstract No. 164625, NAGASE, H. et al., 'Preparation of morphinian derivatives as analgesics and diuretics.' WO 9315081 A1, 05 August 1993.	1-22

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

03 DECEMBER 1998

Date of mailing of the international search report

20 JAN 1999

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/21054

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr., Vol.125, No.17, 21 October 1996 (Columbus, OH, USA), page 1172, column 2, the abstract No. 222432, AMPARO, E.C. et al., 'Preparation of .alpha.-aminoboronic acid and ester as inhibitors of thrombin.' WO 9620689 A2, 11 July 1996.	1-22
Y	Chem. abstr., Vol.126, No.3, 20 January 1997 (Columbus, OH, USA), page 594, column 1, the abstract No. 31466, AMPARO, E.C. et al., 'Boronic acid and ester inhibitors of thrombin.' US Patent 5563127 A, 08 October 1996.	1-22
Y	EP 0 604 183 A1 (ELI LILLY AND COMPANY) 29 June 1994, page 1, abstract.	1-22